

PTEN controls beta-cell regeneration in aged mice by regulating cell cycle inhibitor p16ink4a.

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Public Summary:

This manuscript investigated how growth of beta-cells are controlled in adult pancreas. Beta-cells located in the pancreas produces insulin and is critical for the maintaining blood levels of glucose in healthy individuals. Using mouse models that we engineered to lack a protein (PTEN) that controls the growth potential of the cells, we have found that we can increase the total number of beta cells and make the mice better at handling high glucose levels. In this manuscript, we further found that this effect of PTEN is particularly obvious in the old beta-cells. This finding is very important to Diabetes which often develops in middle-aged and older populations. We also discovered that PTEN controls the levels of a protein that is responsible for the lack of growth in aged beta-cells.

Scientific Abstract:

Tissue regeneration diminishes with age, concurrent with declining hormone levels including growth factors such as insulin-like growth factor-1 (IGF-1). We investigated the molecular basis for such decline in pancreatic beta-cells where loss of proliferation occurs early in age and is proposed to contribute to the pathogenesis of diabetes. We studied the regeneration capacity of beta-cells in mouse model where PI3K/AKT pathway downstream of insulin/IGF-1 signaling is upregulated by genetic deletion of Pten (phosphatase and tensin homologue deleted on chromosome 10) specifically in insulin-producing cells. In this model, PTEN loss prevents the decline in proliferation capacity in aged beta-cells and restores the ability of aged beta-cells to respond to injury-induced regeneration. Using several animal and cell models where we can manipulate PTEN expression, we found that PTEN blocks cell cycle re-entry through a novel pathway leading to an increase in p16(ink4a), a cell cycle inhibitor characterized for its role in cellular senescence/aging. A downregulation in p16(ink4a) occurs when PTEN is lost as a result of cyclin D1 induction and the activation of E2F transcription factors. The activation of E2F transcriptional factors leads to methylation of p16(ink4a) promoter, an event that is mediated by the upregulation of polycomb protein, Ezh2. These analyses establish a novel PTEN/cyclin D1/E2F/Ezh2/p16(ink4a) signaling network responsible for the aging process and provide specific evidence for a molecular paradigm that explains how decline in growth factor signals such as IGF-1 (through PTEN/PI3K signaling) may control regeneration and the lack thereof in aging cells.

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